PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:

VOSSIUS & PARTNER
Siebertstrasse 4
81675 München
ALLEMAGNE

EINGEGANGEN
Vossius & Partner
26. Jan. 2001
Frist
bearb.:

PCT

NOTIFICATION OF TRANSMITTAL OF
THE INTERNATIONAL PRELIMINARY
EXAMINATION REPORT
(PCT Rule 71.1)

Date of mailing *(day/month/year)*	25.01.2001
Applicant's or agent's file reference D 2234 PCT	**IMPORTANT NOTIFICATION**

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/07604	11/10/1999	13/10/1998

Applicant
MAX-PLANCK-GES. ZUR FÖRD. DER WISSENSCHAFTEN E.V.

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. **REMINDER**

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices) (Article 39(1)) (see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Sülberg, A Tel.+49 89 2399-7548

Form PCT/IPEA/416 (July 1992)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
D 2234 PCT		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/07604	11/10/1999	13/10/1998
International Patent Classification (IPC) or national classification and IPC C12N15/12		
Applicant MAX-PLANCK-GES. ZUR FÖRD. DER WISSENSCHAFTEN E.V.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 4 sheets, including this cover sheet.

   ☒ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of 6 sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
27/04/2000	25.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Petri, B Telephone No. +49 89 2399 7356

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07604

I. Basis of the report

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-51 as originally filed

Claims, No.:

1-37 as received on 11/12/2000 with letter of 11/12/2000

Drawings, sheets:

1/18-18/18 as originally filed

Sequence listing part of the description, pages:

1-40, as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☒ contained in the international application in written form.
- ☒ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:
- ☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-37
	No:	Claims	
Inventive step (IS)	Yes:	Claims	1-37
	No:	Claims	
Industrial applicability (IA)	Yes:	Claims	1-37
	No:	Claims	

2. Citations and explanations
   see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

The present application relates to point mutations at a particular position of glutamate receptors of the AMPA-type, which block the desensitizing properties of these receptors. These mutations were not known from the prior art. As furthermore no indication in the available prior art suggested to modify these receptors at that particular position in order to obtain receptors with blocked desensitizing properties, the subject-matter of claims 1-37 is considered novel and inventive.

Claims

1. A nucleic acid molecule encoding a (poly)peptide which has an amino acid sequence of a glutamate receptor of the AMPA-type and/or of a subunit of said receptor and functions as a non-desensitizing AMPA-receptor or as a non-desensitizing subunit thereof, wherein the leucine corresponding to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ is replaced by an aromatic amino acid.

2. The nucleic acid molecule of claim 1 which is

   (a) a nucleic acid molecule comprising a nucleic acid molecule encoding the (poly)peptide having the amino acid sequence of SEQ ID NO: 1, SEQ ID NO: 2, SEQ ID NO: 3, SEQ ID NO: 4, SEQ ID NO: 5, SEQ ID NO: 6, SEQ ID NO: 7, SEQ ID NO:8, SEQ ID NO: 9, or SEQ ID NO: 10, wherein the leucine residue corresponding to position 497 of SEQ ID NO: 1, 5 or 9, corresponding to position 504 of SEQ ID NO: 2, 6 or 10, corresponding to position 507 of SEQ ID NO: 3, to position 505 of SEQ ID NO: 4 or 8, or corresponding to position 513 of SEQ ID NO: 7 is replaced by an aromatic amino acid;

   (b) a nucleic acid molecule comprising a nucleic acid molecule having the DNA sequence of SEQ ID NO: 11, SEQ ID NO. 12, SEQ ID NO: 13, SEQ ID NO: 14, SEQ ID NO: 15, SEQ ID NO: 16, SEQ ID NO: 17, SEQ ID NO: 18, SEQ ID NO: 19 or SEQ ID NO: 20, wherein the codon represented by nnn corresponds to a codon coding for an aromatic amino acid;

   (c) a nucleic acid molecule hybridizing to the complementary strand of a nucleic acid molecule of (a) or (b);

(d) a nucleic acid molecule being degenerate as a result of the genetic code to the nucleotide sequence of a nucleic acid molecule as defined in (c).

3. The nucleic acid molecule of claim 1 or 2 wherein the (poly)peptide comprises an aromatic amino acid at position 497 of SEQ ID NO: 1, 5 or 9, at position 504 of SEQ ID NO: 2, 6 or 10, at position 507 of SEQ ID NO: 3, at position 505 of SEQ ID NO: 4 or 8 or at position 513 of SEQ ID NO: 7, but differs therefrom by at least one mutation selected from the group consisting of amino acid substitutions, addition(s) insertions, deletions, inversions and/or duplications.

4. The nucleic acid molecule of any one of claims 1 to 3 derived from a rat, a mouse or a human.

5. The nucleic acid molecule of any one of claims 1 to 4, wherein said aromatic amino acid residue is tyrosine, phenylalanine, tryptophan or histidine.

6. The nucleic acid molecule of any one of claims 1 to 5 which is DNA, RNA or PNA.

7. The nucleic acid molecule of any one of claims 1 to 6 encoding a fusion protein.

8. A vector comprising the nucleic acid molecule of any one of claims 1 to 7.

9. A vector of claim 8 which is an expression vector, a gene targeting vector and/or a gene transfer vector.

10. A host transformed with a vector of claim 8 or 9 or comprising the nucleic acid molecule of claim 1 to 7.

11. The host of claim 10 which is a mammalian cell, an amphibian cell, an insect cell, a fungal cell, a plant cell or a bacterial cell.

12. The host of claim 11, wherein said mammalian cell is a HEK cell.

13. The host of claim 11, wherein said amphibian cell is an oocyte.

14. The host of claim 13, wherein said oocyte is a frog oocyte.

15. The host of claim 10 which is a non-human transgenic organism.

16. The host of claim 15, wherein said non-human organism is a mammal, amphibian, an insect, a fungus or a plant.

17. A method for producing the (poly)peptide encoded by a nucleic acid molecule of any one of claims 1 to 7 comprising culturing/raising the host of any one of claims 10 to 16 and isolating the produced (poly)peptide.

18. A (poly)peptide encoded by the nucleic acid molecule of any one of claims 1 to 7 or produced by the method of claim 17.

19. An antibody specifically directed to the (poly)peptide of claim 18, wherein said antibody specifically reacts with an epitope comprising the aromatic amino acid which replaces the leucine at position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of said wildtype rat AMPA receptor $GluR1_{flip}$.

20. The antibody of claim 19 which is a monoclonal antibody.

21. A composition comprising the nucleic acid molecule of any one of claims 1 to 7, the vector of claim 8 or 9, the (poly)peptide of claim 18 and/or the antibody of claim 19 or 20.

22. The composition of claim 21 which is a pharmaceutical composition, optionally further comprising a pharmaceutically acceptable carrier and/or diluent and/or excipient.

23. The composition of claim 21 which is a diagnostic composition, optionally further comprising suitable means for detection.

24. A method for the blocking of desensitization of a glutamate receptor of the AMPA-type, comprising the step of replacing a leucine corresponding to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor $GluR1_{flip}$ by an aromatic amino acid.

25. A method for identifying molecules which are capable of interacting with glutamate receptors of the AMPA-type, comprising the steps of

(a) contacting a non-desensitizing AMPA-receptor as encoded by a nucleic acid molecule of any one of claims 1 to 7, a vector of claims 8 or 9, a host of any one of claims 10 to 16, or an antibody of claim 19 or 20 with said molecule; and

(b) identifying among these molecules the molecules which are capable of interacting with said glutamate receptors of the AMPA-type.

26. A method for the characterization of molecules which are capable of interaction with glutamate receptors of the AMPA-type, comprising the steps of

(a) contacting a non-desensitizing AMPA-receptor as defined in any one of claims 1 to 7, a vector of claims 8 or 9, a host of any one of claims 10 to 16, or an antibody of claim 19 or 20 with said molecules; and

(b) measuring and/or detecting the characteristic effect said molecules evoke.

27. A method of screening for molecules which are capable of interacting with glutamate receptors of the AMPA-type, comprising the steps of

(a) contacting a non-desensitizing AMPA-receptor as encoded by a nucleic acid molecule of any one of claims 1 to 7, a vector of claim 8 or 9 or a host of any one of claims 10 to 16 with a candidate molecule; and

(b) measuring and/or detecting a response; and

(c) comparing said response to a standard response as measured in the absence of said candidate molecule.

28. A method for the production of a pharmaceutical composition comprising the steps of the method of any one of claims 25 to 27 and comprising a further step, wherein a derivative of said identified, characterized and/or screened molecule is generated.

29. A method for the production of a pharmaceutical composition comprising the steps of the method of any one of claims 25 to 28 and formulating the molecules identified, characterized, screened and/or derivatized in pharmaceutically acceptable form.

30. The method of any one of claims 25 to 29, wherein said molecule(s) comprise(s) (a) neuroprotective and/or (a) nootropic molecule(s).

31. The method of any one of claims 25 to 30, wherein said molecule(s) comprise(s) antagonist(s), partial antagonist(s), partial agonist(s) and/or agonist(s) for glutamate receptors.

32. Use of a non-desensitizing AMPA-receptor as encoded by the nucleic acid molecule of any one of claims 1 to 7 or use of a host as defined in any one of claims 10 to 16 as a biosensor for glutamate concentrations

33. Use of a non-desensitizing AMPA-receptor as encoded by the nucleic acid molecule of any one of claims 1 to 7 or use of a host as defined in any one of claims 10 to 16 for the characterization of glutamate receptor channel properties.

34. Use of a nucleic acid molecule of any one of claims 1 to 7, of a vector of claims 8 or 9, of a host of claims 10 or 11, of a (poly)peptide of claim 18, and/or of the antibody of claim 19 or 20 for the preparation of a pharmaceutical composition for preventing and/or treating neurological and/or neurodegenerative disorders.

35. The use of claim 33, wherein said neurological and/or neurodegenerative disorders are selected from the group consisting of Alzheimer's disease, Parkinson's disease, Huntington's disease, amyotrophic lateral sclerosis (FALS/SALS), ischemia, stroke, epilepsy, AIDS dementia and learning disorders.

36. Use of the nucleic acid molecule of any one of claims 1 to 7, the vector of claim 8 or 9, the host cell of claim 10 or 11 in gene therapy.

37. A kit comprising the nucleic acid molecule of any one of claims 1 to 7, the vector of claim 8 or 9, the host of any one of claims 11 to 16, the (poly)peptide of claim 18, the antibody of claim 19 or 20 or the molecule as identified, characterized or screened in any one of claims 25 to 31.

PATENT COOPERATION TREA

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
VOSSIUS & PARTNER
Siebertstrasse 4
81675 München
GERMANY

EINGEGANGEN
Vossius & Partner
13. April 2000
Frist
bearb.:

Applicant's or agent's file reference D 2234 PCT	Date of mailing *(day/month/year)* 10/04/2000
	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/EP 99/ 07604	International filing date *(day/month/year)* 11/10/1999
Applicant ROSENMUND, CHRISTIAN et al.	

1. [X] The applicant is hereby notified that the International Search Report has been established and is transmitted herewith.

Filing of amendments and statement under Article 19:
The applicant is entitled, if he so wishes, to amend the claims of the International Application (see Rule 46):

When? The time limit for filing such amendments is normally 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

Where? Directly to the International Bureau of WIPO
34, chemin des Colombettes
1211 Geneva 20, Switzerland
Fascimile No.: (41–22) 740.14.35

For more detailed instructions, see the notes on the accompanying sheet.

2. [ ] The applicant is hereby notified that no International Search Report will be established and that the declaration under Article 17(2)(a) to that effect is transmitted herewith.

3. [ ] **With regard to the protest** against payment of (an) additional fee(s) under Rule 40.2, the applicant is notified that:

[ ] the protest together with the decision thereon has been transmitted to the International Bureau together with the applicant's request to forward the texts of both the protest and the decision thereon to the designated Offices.

[ ] no decision has been made yet on the protest; the applicant will be notified as soon as a decision is made.

4. **Further action(s):** The applicant is reminded of the following:

Shortly after **18 months** from the priority date, the international application will be published by the International Bureau. If the applicant wishes to avoid or postpone publication, a notice of withdrawal of the international application, or of the priority claim, must reach the International Bureau as provided in Rules 90*bis*.1 and 90*bis*.3, respectively, before the completion of the technical preparations for international publication.

Within 19 months from the priority date, a demand for international preliminary examination must be filed if the applicant wishes to postpone the entry into the national phase until 30 months from the priority date (in some Offices even later).

Within 20 months from the priority date, the applicant must perform th prescribed acts for entry into the national phase before all designated Offices which hav not been lected in th demand or in a later election within 19 months from the priority date or could not be lected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL–2280 HV Rijswijk Tel. (+31–70) 340–2040, Tx. 31 651 epo nl, Fax: (+31–70) 340–3016	Sandra De Jong-van Dam

Form PCT/ISA/220 (July 1998)

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
D 2234 PCT		
International application No.	International filing date *(day/month/year)*	(Earliest) Priority Date *(day/month/year)*
PCT/EP 99/07604	11/10/1999	13/10/1998
Applicant		
ROSENMUND, CHRISTIAN et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 6 sheets.

[X] It is also accompanied by a copy of each prior art document cited in this report.

1. **Basis of the report**

   a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

   [ ] the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

   b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing :

   [X] contained in the international application in written form.

   [X] filed together with the international application in computer readable form.

   [ ] furnished subsequently to this Authority in written form.

   [ ] furnished subsequently to this Authority in computer readble form.

   [X] the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

   [ ] the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. [X] **Certain claims were found unsearchable** (See Box I).

3. [ ] **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

   [X] the text is approved as submitted by the applicant.

   [ ] the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

   [ ] the text is approved as submitted by the applicant.

   [X] the text has been established, according to Rul 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from th date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with th abstract is Figure No. –

   [ ] as suggested by the applicant.

   [ ] because the applicant failed to suggest a figure.

   [ ] because this figure better characterizes the invention.

   [ ] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/EP 99/07604

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C12N15/12 C12N5/10 C07K14/705 C07K16/28 A61K31/70
A61K38/17 A61K39/395 A01K67/027 G01N33/50 A61P25/00

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C12N C07K A61K A01K G01N A61P

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	STERN-BACJ Y. ET AL.: "A point mutation in the glutamate binding site blocks desensitization of AMPA receptors" NEURON, vol. 21, October 1998 (1998-10), pages 907-918, XP000891606 the whole document ---	1-37
A	STERN-BACH Y. ET AL.: "Agonist selectivity of glutamate receptors is specified by two domains structurally related to bacteria amino acid-binding proteins" NEURON, vol. 13, 1994, pages 1345-1357, XP000891623 cited in the application the whole document ---	1-37

-/--

[X] Further documents are listed in the continuation of box C.

[X] Patent family members are listed in annex.

° Special categories of cited documents :

"A" document defining the general state of the art which is not considered to be of particular relevance

"E" earlier document but published on or after the international filing date

"L" document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

"O" document referring to an oral disclosure, use, exhibition or other means

"P" document published prior to the international filing date but later than the priority date claimed

"T" later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
29 March 2000	10/04/2000

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Galli, I

2

Form PCT/ISA/210 (second sheet) (July 1992)

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	PARTIN K. M. ET AL.: "AMPA receptor flip/flop mutants affecting deactivation, desensitization, and modulation by cyclothiazide, aniracetam, and thiocyanate" J. NEUROSCI., vol. 16, no. 21, 1 November 1996 (1996-11-01), pages 6634-6647, XP002134206 cited in the application the whole document	1-37
A	UCHINO S. ET AL.: "Mutations in a putative agonist binding region of the AMPA-selective glutamate receptor channel" FEBS LETTERS, vol. 308, no. 3, 24 August 1992 (1992-08-24), pages 253-257, XP002134207 the whole document	1-37
A	EP 0 574 257 A (KAMBOJ RAJENDER ;ELLIOTT CANDACE (CA); NUTT STEPHEN L (CA)) 15 December 1993 (1993-12-15) abstract claims 1-18	1-37

2

INTERNATIONAL SEARCH REPORT

[redacted]ation on patent family members

[redacted]rnational Application No
[redacted]CT/EP 99/07604

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0574257 A	15-12-1993	CA 2098054 A	11-12-1993
		JP 6205679 A	26-07-1994
		MX 9303444 A	29-07-1994
		US 5610032 A	11-03-1997

INTERNATIONAL SEARCH REPORT

International application No.
PCT/EP 99/07604

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Remark: Although claim 36 directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.: 28-31
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
See FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark n Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Claims Nos.: 28-31

Claims 28-31 refer to methods for the production of a pharmaceutical composition comprising ligands of the non-desensitizing AMPA receptors. However, said claims do not give a true technical charactrization of said ligands. Moreover, no such compounds are defined in the application. In consequence, insofar as said claims are characterized essentially by said ligands, their scope is ambiguous and vague, and their subject-matter is not sufficiently disclosed and supported (Art. 5 and 6 PCT). No search can be carried out for such purely speculative claims whose wording is, in fact, a mere recitation of the results to be achieved.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

Box III TEXT OF THE ABSTRACT (Continuation of item 5 of the first sheet)

The present invention relates a glutamate receptor of the AMPA-type which functions as a non-desensitizing AMPA-receptor or as a non-desenstizing subunit thereof, wherein the leucine corresponding to position 497 of the wildtype rat AMPA-receptor FluRflip, or the leucine at the equivalent position in other glutamate receptors of the AMPA-type, is replaced by an aromatic amino acid.

PCT WORLD INTELLECTUAL PROPERTY ORGANIZATION
International Bureau

INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 15/12, 5/10, C07K 14/705, 16/28, A61K 31/70, 38/17, 39/395, A01K 67/027, G01N 33/50, A61P 25/00

A2

(11) International Publication Number: **WO 00/22118**

(43) International Publication Date: 20 April 2000 (20.04.00)

(21) International Application Number: PCT/EP99/07604

(22) International Filing Date: 11 October 1999 (11.10.99)

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(54) Title: NON-DESENSITIZING AMPA-RECEPTORS

(57) Abstract

The present invention relates to a nucleic acid molecule encoding a (poly)peptide which has an amino acid sequence of a glutamate receptor of the AMPA-type and functions as a non-desensitizing AMPA-receptor or as a non-desensitizing subunit thereof, wherein the leucine corresponding to position 497 of the wildtype rat AMPA-receptor GluR1$_{flip}$ or the leucine at the position which corresponds in other glutamate receptors of the AMPA-type by comparison of homology to position 497 of the wildtype rat AMPA-receptor GluR1$_{flip}$ is replaced by an aromatic amino acid. The invention further relates to (poly)peptides encoded by said nucleic acid molecules, vectors and hosts comprising said nucleic acid molecules, as well as to methods for producing (poly)peptides encoded by said nucleic acid molecules. The present invention also provides for antibodies specifically directed to (poly)peptides encoded by said nucleic acid molecules. Additionally, the invention relates to a method for the blocking of desensitization of a glutamate receptor of the AMPA-type, comprising the step of replacing a leucine which corresponds by comparison of homology to position 497 of the rat AMPA-receptor GluR1 by an aromatic amino acid and methods for identifying and/or characterizing molecules which are capable of interaction with glutamate receptors of the AMPA type. The invention also relates to the one of the aforementioned nucleic acid molecules, (poly)peptides, hosts, vectors and/or antibodies as biosensors, for the characterization of glutamate receptor channel properties and/or for the preparation of pharmaceutical compositions. Furthermore, the invention provides for pharmaceutical compositions, diagnostics and kits comprising and/or employing the compounds of the invention.

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